PATENT
Docket No. 219002030901

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

George F. SCHREINER, *et al.*

Serial No.: 10/083,817

Filing Date: 26 February 2002

For: METHODS OF TREATING HYPERTENSION AND COMPOSITIONS FOR USE THEREIN

Examiner: Christine J. Saoud

Group Art Unit: 1647

DECLARATION OF GEORGE F. SCHREINER, M.D., PH.D.

UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, George F. Schreiner, declare as follows:

1. I am Senior Vice President of Scios Research & Development and Chief Scientific & Medical Officer at Scios, Inc., the assignee of the present application. I hold a M.D. from Harvard Medical School and a Ph.D. in Immunology from Harvard University. I have been working in the field of cardiovascular disease and nephrology for over 24 years. A copy of my *curriculum vitae* is attached (Exhibit 3).

2. In accordance with standard procedures recognized as significant by workers in the field of hypertension, the effect of administering vascular endothelial growth factor to animals presenting elevated blood pressure as a result of the expression of the VEGF receptor sFlt(1-3) was observed as described below.

3. An adenovirus was engineered to express the soluble VEGF receptor sFlt(1-3). This construct expresses the first three IgG-like domains of sFlt-1. The expressed portion of the

receptor includes the VEGF binding domain but omits domains 4-6, which include the regions responsible for receptor dimerization. A schematic of Flt-1 and the soluble form, sFlt-1, is shown in Exhibit 1A. Sequence analysis of the mouse and human Flt-1 and sFlt-1 at the truncation site that makes the receptor soluble is shown in Exhibit 1B.

4. The engineered adenovirus was used to infect a control group and a treated group, with six rats in each group. Both groups were injected in the tail vein with 1×10^9 plaque forming units (pfu) of the adenovirus engineered to express sFlt(1-3). On the second day after viral injection, animals were randomized to receive $VEGF_{121}$ (100 mg/kg body weight) or phosphate buffered saline (PBS) subcutaneously twice a day for 7 days. On the 7th day after the morning VEGF injection, animals were cannulated for blood pressure measurement and blood was drawn. Plasma samples were analyzed for the presence of sFlt(1-3) and to detect free VEGF using an ELISA assay (data not shown).

5. Blood pressure measurements were taken from the animals in each group. Rats have a resting systolic pressure of about 120 mmHg and a resting diastolic pressure of about 84 mmHg. As shown in Exhibit 2, animals in the control group had elevated systolic and diastolic blood pressures. Animals treated with VEGF showed reduced blood pressure relative to the control group. The blood pressure measurements from the control group of rats approached normal levels. . All rats involved in the study were maintained on a diet of standard rat chow, which is low in dietary salt.

6. The results provided above demonstrate that VEGF is a useful in lowering blood pressure in an animal model of hypertension that is not salt-dependent.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Raritan, NJ on 01 03 2004.
(city) (state) (day) (month)

George F. Schreiner, M.D., Ph.D.

EXHIBIT 1

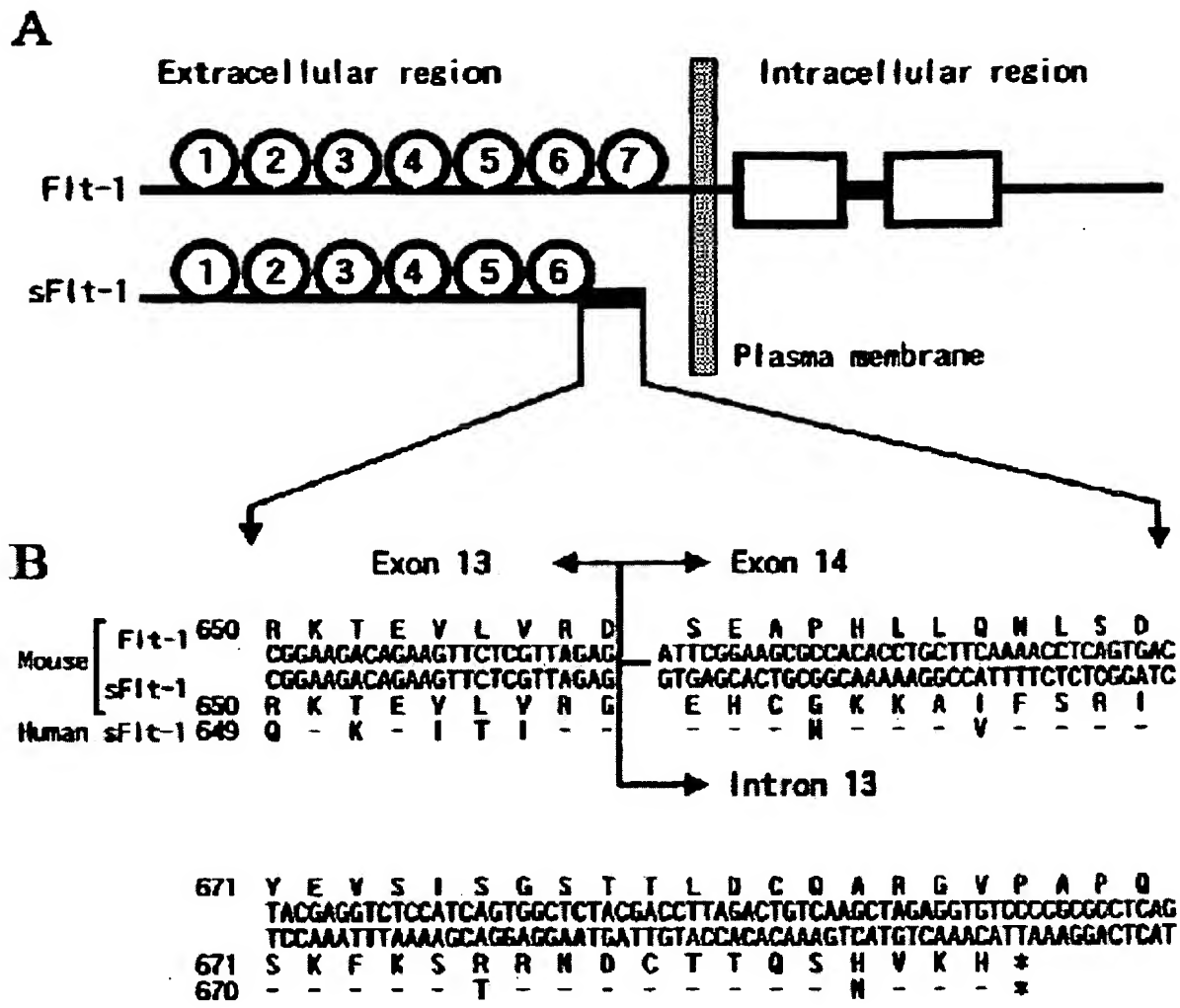
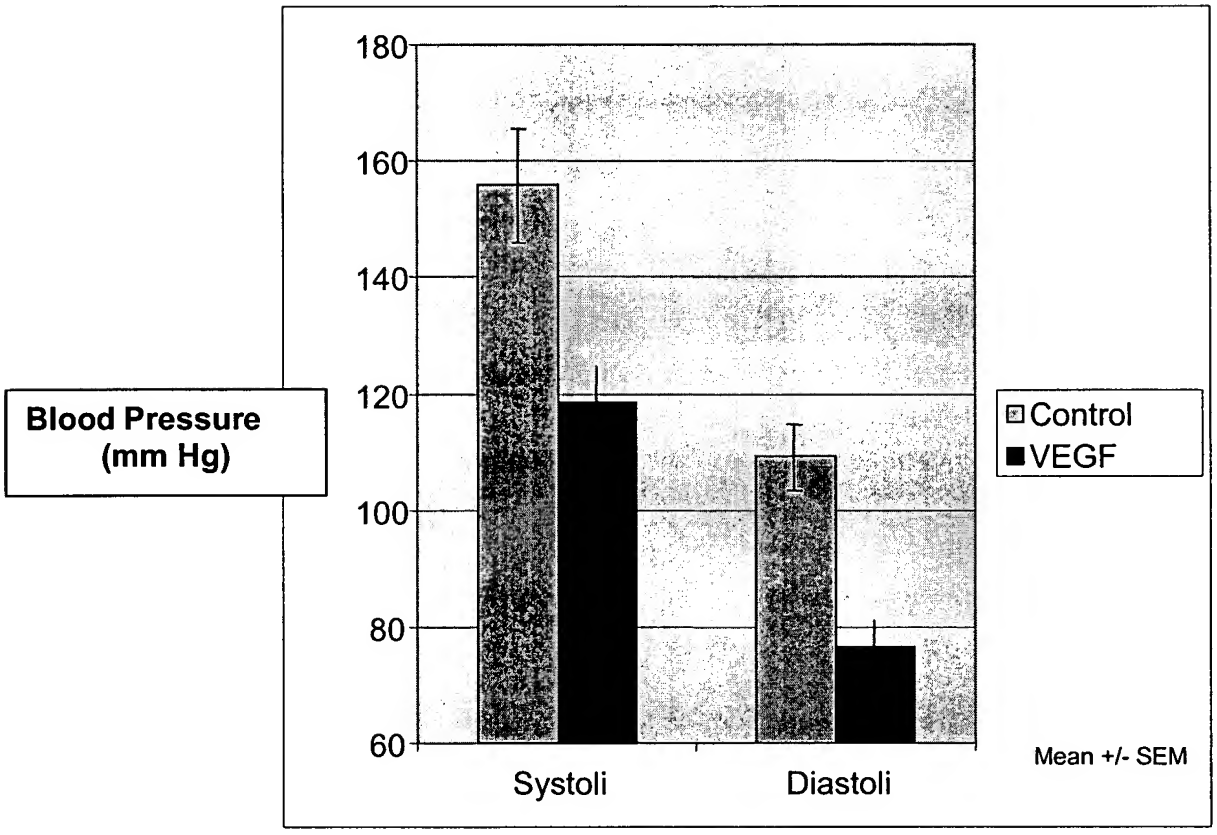

A
Extracellular region
Intracellular region
Flt-1
1 2 3 4 5 6 7
sFlt-1
1 2 3 4 5 6
Plasma membrane
B
Exon 13
Exon 14
Intron 13
Mouse Flt-1 650 R K T E V L V R D S E A P H L L Q H L S D
CGGAAGACAGAAGTTCTCGTTAGAG ATTCGGAAGCGCCACACCTGCTTCAAAACCTCAGTGAC
Mouse sFlt-1 CGGAAGACAGAAGTTCTCGTTAGAG GTGAGCACTGCGGCAAAAAGGCCATTTTCTCTCGGATC
650 R K T E V L V R G E H C G K K A I F S R I
Human sFlt-1 649 Q - K - I T I - - - - - H - - - V - - - -
671 Y E V S I S G S T T L D C Q A R G V P A P Q
TACGAGGTCTCCATCAGTGGCTCTACGACCTTAGACTGTCAAGCTAGAGGTGTCCCGCGCCTCAG
TCCAAATTTAAAAGCAGGAGGAATGATTGTACCACACAAAGTCATGTCAAACATTAAAGGACTCAT
671 S K F K S R R H D C T T Q S H V K H *
670 - - - - - T - - - - - - - - N - - - *

EXHIBIT 2


Blood Pressure (mm Hg)
180
160
140
120
100
80
60
Systoli
Diastoli
Control
VEGF
Mean +/- SEM

George F. Schreiner

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Los Altos Hills, CA 94022
(650)-941-5123

EDUCATION

1971	A.B.	Harvard College, Cambridge, Massachusetts
1977	M.D.	Harvard Medical School, Boston, Massachusetts
1977	Ph.D.	Harvard University, Cambridge, Massachusetts (Immunology)

PROFESSIONAL EXPERIENCE

8/00-
Scios Inc.
CHIEF SCIENTIFIC OFFICER AND VICE PRESIDENT

Responsibilities: (a) All research operations, including medicinal chemist
(b) Preclinical development of drug candidates
(c) Strategic clinical development of novel drug candidates
(d) Development of new indications for currently marketed drugs

1/97-8/00
Scios Inc.
VICE PRESIDENT OF CARDIORENAL RESEARCH
CORPORATE MANAGEMENT COMMITTEE

Responsibilities: (a) Established disease-based research program focusing on inflammation, cardiac and pulmonary diseases, and progressive renal failure.
(b) Technical supervision of functional genomics, molecular and cellular biology, pharmacology, pathology, high throughput screening, preclinincal development.
(b) Established focus on small molecule kinase inhibitors and recombinant protein therapeutics

1/95-1/97
CV Therapeutics Inc.
VICE PRESIDENT, MEDICAL SCIENCE AND PRECLINICAL RESEARCH

1/933-1/95
CV Therapeutics Inc
VICE PRESIDENT, MEDICAL SCIENCE

ACADEMIC APPOINTMENTS

1980-1982	Instructor in Pathology, Department of Pathology, Harvard Medical School, Boston, Massachusetts
1982-1985	Assistant Professor of Pathology, Department of Pathology, Harvard Medical School, Boston, Massachusetts
1983-1985	Assistant Professor of Medicine, Brigham and Women's Hospital Harvard Medical School, Boston, Massachusetts
1985-1989	Assistant Professor of Medicine and Pathology Washington University School of Medicine St. Louis, Missouri
1989-1993	Associate Professor of Medicine and Pathology Washington University School of Medicine St. Louis, Missouri
1993-1997	Consulting Professor of Medicine, Stanford University Palo Alto, California

POSTDOCTORAL TRAINING

1977-1980	Medical Resident, Peter Bent Brigham Hospital, Boston, Massachusetts
1982-1983	Fellow, Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

RESEARCH FELLOWSHIPS

1973-1974	Fellow, Karen Grunebaum Foundation
1977-1980	Research Fellow, Department of Pathology, Harvard Medical School, Boston, Massachusetts
1980-1982	Fellow, Arthritis Foundation

CERTIFICATION

American Board of Medicine
Internal Medicine
Nephrology

HONORS/AWARDS/OFFICES

1985	Established Investigator, American Heart Association
1989-1990	Chairman, Midwest Section, American Federation for Clinical Research
1989-1990	Co-Chairman, Public Policy Committee, American Federation for Clinical Research
1990	American Society for Clinical Investigation
1991-1992	Chairman, Public Policy Committee, American Federation for Clinical Research
1992	Member, Council on Glomerular Diseases, National Kidney Foundation
1991-1996	Assistant Editor, American Journal of Kidney Diseases

HOSPITAL APPOINTMENTS

1980-1985	Junior Associate in Medicine, Brigham and Women's Hospital, Boston, Massachusetts
1986-1993	Associate Physician, Barnes Hospital, St. Louis, Missouri
1986-1988	Assistant Director of the Renal Transplant Service, Department of Medicine, Barnes Hospital, St. Louis, Missouri

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

1978	American Association of Immunologists
1982	The American Society of Nephrology
1982	American Society of Pathologists
1983	International Society of Nephrology
1987	American Federation for Clinical Research
1988	National Kidney Foundation
1990	American Society for Clinical Investigation

PATENTS

US 5,631,260	Xanthine epoxides as A.Sub.1 adenosine receptor agonists and antagonists
US 5,663,450	Macrophage lipid chemoattractant
US 5,668,139	A1 adenosine receptor agonists and antagonists
US 5,789,416	N.sup.6 mono heterocyclic substituted adenosine derivatives
US 5,840,875	Kidney Na/PO.sub.4 cotransporter antisense oligonucleotide
US 5,869,537	Macrophage lipid chemoattractant
US 6,130,235	Compounds and methods to treat cardiac failure and other disorders
US 6,184,226	Quinazoline derivatives as inhibitors of p-38 alpha.
US 6,277,989	Quinazoline derivatives as medicaments
US 6,340,685	Compounds and methods to treat cardiac failure and other disorders
US 6,342,495	Agonists and antagonists of peripheral-type benzodiazepine receptors
US 6,352,975	Methods of treating hypertension and compositions for use therein
US 6,380,183	Treatment of diseases involving cyst formation
US 6,410,540	Inhibitors of p38 alpha kinase
US 6,340,685 B1	Compounds to treat cardiac failure
US 6,541,477 B2	Inhibitors of p38-alpha kinase
US 6,589,954 B1	Compounds and methods to treat cardiac failure and other disorders
US 6,677,300 B1	Treatment of Microvascular Angiopathies

Patents Pending: 7

PUBLICATIONS

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2. Unanue, E.R. and Schreiner, G.F. 1975. The modulation of immunoglobulin in B lymphocytes and its relevance to immune stimulation. In: Rosenthal, A.S., ed. Immune Recognition. New York, New York: Academic Press, Inc. p. 261-280.
3. Unanue, E.R., Ault, K.A., Schreiner, G.F. and Sidman, C.L. 1975. The cycle of ligand-induced changes in B cells-functional relationship. In: Seligmann, M., Preud'homme, J.L., Kourilsky, F.M., eds. Membrane Receptors of Lymphocytes. Amsterdam, Holland: North-Holland Publishing Company, p.363-372.
4. Schreiner, G.F. and Unanue, E.R. 1975. Anti-Ig-triggered movement of lymphocytes: specificity and lack of evidence for directional migration. *J. Immuno.* 114(2 Pt 2):809-814.
5. Schreiner, G.F. and Unanue, E.R. 1976. Membrane and cytoplasmic changes in B lymphocytes induced by ligand-surface immunoglobulin interactions. *Adv. Immuno.* 24:37-165.
6. Schreiner, G.F. and Unanue, E.R. 1976. Calcium-sensitive modulation of Ig capping: evidence supporting a cytoplasmic control of ligand-receptor complexes. *J. Exp. Med.* 143(1):15-31.
7. Schreiner, G.F and Unane, E.R. 1976. The disruption of immunoglobulin caps by local anesthetics. *Clin. Immunol. Immunopathol.* 6(2):264-269.
8. Schreiner, G.F., Braun, J. and Unanue, E.R. 1976. Spontaneous redistribution of surface immunoglobulin in the motile B lymphocyte. *J. Exp. Med.* 114:1683-1688.
9. Unanue, E.R. and Schreiner, G.F. 1977. Structure and function of surface immunoglobulin of lymphocytes. In: Poste, G. and Nicolson, G. eds., Dynamic Aspects of Cell Surface Organization. Elsevier/North-Holland Biomedical Press. p.619-641.
10. Schreiner, G.F., Fujiwara, K., Pollard, T.D. and Unanue, E.R. 1977. Redistrubution of myosin accompanying capping of surface lg. *J. Exp. Med.* 145(5):1393-1398.
11. Ward, P.A., Unanue, E.R., Goralnick, S. and Schreiner, G.F. 1977. Chemotaxis of rat lymphocytes. *J. Immunol.* 119(2):416-421.
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13. Schreiner, G.F., Cotran, R.S., Pardo, V. and Unanue, E.R. 1978. A mononuclear cell component in experimental immunological glomerulonephritis. *J. Exp. Med.* 147(2):367-384.
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15. Schreiner, G.F., Cotran, R.S. and Unanue, E.R. 1981. Glomerular cells and immune function. In: Zurukzoglu, W., Papdimitriou, M., Pyrpasopoulos, M., Sion, M., Zamboulis, C., eds. Proceedings of the Eight International Congress of Nephrology: Advances in Basic and Clinical Nephrology. Basel, Switzerland: S. Karger. 858.
16. Schreiner, G.F., Kiely, J.M, Cotran, R.S. and Unanue, E.R. 1981. Characterization of resident glomerular cells in the rat expressing Ia determinants and manifesting genetically restricted interactions with lymphocytes. *J. Clin. Invest.* 68(4):920-921.

17. Unanue, E.R., Schreiner, G.F. and Cotran, R.S. 1982. A role of mononuclear phagocytes in immunologically induced glomerulonephritis. In: Cummings, N., Michael, A., Wilson, C., Immune Mechanisms in Renal Disease. New York, NY: Plenum Publishing Corporation. 443-445.
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43. Rovin, B.H., Lefkowith, J.B and Schreiner, G.F. 1990. Mechanisms underlying the anti-inflammatory effects of essential fatty acid deficiency in experimental glomerulonephritis: Inhibited release of a monocyte chemoattractant by glomeruli. *J. Immuno.* 145(4):1238-1245.
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